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(54) (TITLE OF THE INVENTION) AQUEOUS SKIN EXTERNAL PREPARATION COMPOSITION

(57) (ABSTRACT)
(PROBLEM) The present invention provides a homogeneous aqueous skin external preparation composition that is stable, does not irritate the skin, has excellent antiseptic power and contains an anti-inflammatory agent.
(MEANS FOR SOLVING) A homogeneous aqueous skin external preparation composition containing:
(A) an anti-inflammatory agent;
(B) one or more types of substances selected from an aliphatic alcohol having an unsaturated hydrocarbon group with a carbon number of 12 to 20, a fatty acid having an unsaturated hydrocarbon group with a carbon number of 12 to 20, and/or a salt or ester thereof; and
(C) a preservative;
wherein the content of monovalent lower alcohol with a carbon number of 1 to 6 is at most 70% mass percent.

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(SCOPE OF PATENT CLAIMS)

(CLAIM 1) A homogenous aqueous skin external preparation composition, characterized in that it contains (A) an anti-inflammatory agent, (B) one or more types of substances selected from an aliphatic alcohol having an unsaturated hydrocarbon group with a carbon number of 12 to 20, a fatty acid having an unsaturated hydrocarbon group with a carbon number of 12 to 20, and/or a salt or ester thereof, and (C) a preservative, wherein the content of monovalent lower alcohol with a carbon number of 1 to 6 is at most 70% mass percent.

(CLAIM 2) A homogenous aqueous skin external preparation composition according to Claim 1, characterized in that the aqueous solvent (D) contains a mixture of two or more types of monovalent lower alcohols and water.

(CLAIM 3) A homogenous aqueous skin external preparation composition according to one of Claims 1 or 2, characterized in that it contains (D) an aqueous solvent for which the ratio of monovalent lower alcohol with a carbon number of 1 to 6 to water is 0.7 to 1.4.

(CLAIM 4) A homogenous aqueous skin external preparation composition according to one of Claims 1 through 3, characterized in that (C) is at least one type of preservative selected from dibutylhydroxytoluene, sodium edetate, benzalkonium chloride, citric acid, salicylic acid, isobutyl parahydroxybenzoate, isopropyl parahydroxybenzoate, butyl parahydroxybenzoate, propyl parahydroxybenzoate, methyl parahydroxybenzoate and D-sorbitol.

(CLAIM 5) A homogenous aqueous skin external preparation composition according to one of Claims 1 through 4, characterized in that it further contains one or more types of plant fragrances selected from peppermint oil, spearmint oil, mentha oil, eucalyptus oil, jasmine oil, lavender oil, lemon oil, orange oil, lime oil, mandarin oil, rose oil and rosemary oil and one or more types of synthetic fragrances selected from menthol, borneol, geraniol, linalool, citronellol, nerol, limonene, pinene, camphene, citral, citronellal, cineol, curcumene, sabinic acid, hinokiol and phytol.

(CLAIM 6) A skin external preparation characterized in that an aqueous skin external preparation composition according to one of Claims 1 through 5 with viscosity of 1 to 1000 cp at 25°C is stored in a container having an outflow opening or a discharge opening with a diameter of 0.1 to 5 mm.

(CLAIM 7) A skin external preparation according to Claim 6, characterized in that the main body of the container is made of one or more types of monolayer or multilayer materials selected from polyethylene terephthalate (PET), polypropylene (PP), polyethylene (high-density polyethylene: HPDE, low-density polyethylene: LDPE), glass, polystyrene and metal.

(CLAIM 8) A skin external preparation according to Claim 6 or 7, characterized in that the outflow opening or the discharge opening is made of one or more types of monolayer or multilayer materials selected from polyethylene terephthalate (PET), polypropylene (PP), polyethylene (high-density polyethylene: HPDE, low-density polyethylene: LDPE) and polystyrene.

(CLAIM 9) A skin external preparation characterized in that an aqueous skin external preparation composition according to one of Claims 1 through 5 with viscosity of 500 to 100,000 cp at 25°C is stored in a tube made of a flexible material.

(DETAILED DESCRIPTION OF THE INVENTION)

(0001) (TECHNICAL FIELD OF THE INVENTION) The present invention relates to a homogenous aqueous external preparation composition containing an anti-inflammatory agent.

(0002)

(PRIOR ART) Since many anti-inflammatory agents used for skin external preparations such as anti-inflammatory/analgesic drugs or eczema drugs are poorly water soluble, solution stability becomes a significant issue when forming an aqueous preparation. Performance improving agents such as lipophilic sorbefacients, which are mixed in order to improve the effectiveness of anti-inflammatory agents, also inhibit the stabilization of aqueous preparations. In order to stabilize these in an aqueous composition, there is a method wherein these are dissolved by a large quantity of a lower alcohol to form a homogenous preparation, but this is prone to cause trouble due to skin irritation such as skin degreasing or wound irritation. Therefore, in order to suppress skin irritation, there has been a demand for a stable external preparation containing an anti-inflammatory agent that limits the mixing of lower alcohols. On the other hand, when forming an aqueous preparation for which the amount of lower alcohol mixed is small, there are problems such as inadequate antiseptic power, the adherence of impurities to the mouth, inner plug or cap of the container due to use, and the introduction of secondary contamination.

(0003) (PROBLEM TO BE SOLVED BY THE INVENTION) The present invention provides a homogeneous aqueous skin external preparation composition that is stable, does not irritate the skin, has excellent antiseptic power and contains an anti-inflammatory agent. "Homogeneous" in the present invention refers to a system in which liquid constituents are separated into an oil phase and an aqueous phase or emulsified and dispersed; in other words, a liquid system in the dissolved or soluble state.

(0004)

(MEANS FOR SOLVING THE PROBLEM) As a result of investigations performed by the present inventors, the inventors discovered that the problem described above could be solved by selecting a specific performance improving agent and incorporating a preservative, and they thus completed the present invention. That is, the present invention provides a homogeneous aqueous skin external preparation composition containing:

(A) an anti-inflammatory agent;

(B) one or more types of substances selected from an aliphatic alcohol having an unsaturated hydrocarbon group with a carbon number of 12 to 20, a fatty acid having an unsaturated hydrocarbon group with a carbon number of 12 to 20, and/or a salt or ester thereof; and

(C) a preservative;

wherein the content of monovalent lower alcohol with a carbon number of 1 to 6 is at most 70% mass percent.

(0005) The present invention also provides an aqueous skin external preparation composition in which the aqueous solvent of the above composition is an aqueous solvent for which the ratio of monovalent lower alcohol with a carbon number of 1 to 6 to water is 0.7 to 1.4.

(0006) Further, the present invention provides a skin external preparation in which an aqueous skin external

preparation composition of the present invention with viscosity of 1 to 1000 cp at 25°C is stored in a container having a 0.1 to 5 mm outflow opening or a discharge opening, and a skin external preparation in which an aqueous skin external preparation composition of the present invention with viscosity of 500 to 100,000 cp at 25°C is stored in a tube made of a flexible material.

The present invention will be described in detail hereafter.

(0007)

(EMBODIMENTS OF THE INVENTION) (A) Examples of the anti-inflammatory agent used in the aqueous skin external preparation composition of the present invention are as follows.

Nonsteroidal anti-inflammatory agents such as ketoprofen, indomethacin, bufexamac, ibuprofen, piroxicam, suprofen, flurbiprofen, naproxen, loxoprofen, glycyrrhetinic acid and salts thereof, mefenamic acid, allantoin, methyl salicylate, glycol salicylate and dipotassium glycyrrhetinate, steroidal anti-inflammatory agents such as hydrocortisone, prednisolone and dexamethasone, crude drug extracts such as phellodendron bark, aesculus hippocastanum seed, arnica and matricaria chamomilla, etc.

(0008) Nonsteroidal and crude drug anti-inflammatory agents are preferable. Particularly preferable anti-inflammatory agents are ketoprofen, indomethacin, bufexamac and suprofen. The amount of nonsteroidal anti-inflammatory agent to be mixed is preferably 0.01 to 20 mass percent in the composition and even more preferably 0.1 to 10 mass percent.

(0009) (B) The aliphatic alcohol having an unsaturated hydrocarbon group with a carbon number of 12 to 20, a fatty acid having an unsaturated hydrocarbon group with a carbon number of 12 to 20, and/or a salt or ester thereof used in the aqueous skin external preparation composition of the present invention is used for the purpose of improving the efficacy of non-steroidal anti-inflammatory agents. Specific examples are given below.

(0010) Examples of unsaturated aliphatic alcohols with carbon numbers of 12 to 20 include palmitoleyl alcohol, oleyl alcohol, eicosonyl alcohol, elaidyl alcohol and linoleyl alcohol. Oleyl alcohol, elaidyl alcohol or mixtures thereof are preferable.

(0011) Examples of unsaturated fatty acids with carbon numbers of 12 to 20 and/or salts thereof include oleic acid, elaidic acid, linoleic acid, undecylenic acid, myristoleic acid, palmitoleic acid, lindelic acid, lauroleic acid, tsuzuic acid, petroselinic acid, vaccenic acid and gondoic acid. Oleic acid, elaidic acid or mixtures thereof are preferable.

(0012) Examples of unsaturated fatty acid esters include esters of the above unsaturated fatty acids and monovalent alcohols with carbon numbers of 1 to 18, glycerin and diglycerin. Examples of these esters include isopropyl oleate, glycerin monoleic acid ester glycerin, dioleic acid esters, octyldodecyl oleate and oleyl oleate.

(0013) The content of (B) in the composition is preferably 0.005 to 20 mass percent, more preferably 0.1 to 10 mass percent, and particularly preferably 0.0 to 5 mass percent. Particularly favorable solution stability and drug efficacy can be obtained within this range.

(0014) The preservative used as constituent (C) of the present invention refers to a compound described as a preservative in the "Japanese Pharmaceutical Excipient Directory 2000" (edited by the Japan Pharmaceutical Excipients Council, Yakuji Nippo, Ltd.). Specific examples include benzoic acid, sodium benzoate, benzonium, phenol, sodium edetate, tetrasodium edetate, cetylpyridinium chloride, benzalkonium chloride, benzalkonium chloride solution, benzethonium chloride, chlorhexidine hydrochloride, [catoredine], captan, dried sodium sulfite, citric acid, chlorhexidine gluconate solution, L-potassium glutamate, cresol, m-cresol, chlorocresol, chlorobutanol, salicylic acid, sodium salicylate, dibutylhydroxytoluene, D-sorbitol, sorbic acid, potassium sorbate, thimerosal, thymol, sodium dehydroacetate, concentrated benzalkonium chloride solution 50, normal butyl glycidyl ether, isobutyl parahydroxybenzoate, isopropyl parahydroxybenzoate, ethyl parahydroxybenzoate, butyl parahydroxybenzoate, propyl parahydroxybenzoate, methyl parahydroxybenzoate, human serum albumin, phenylethyl alcohol, phenol, propylene glycol, benzyl alcohol, boric acid, borax, formalin, 2-mercaptobenzimidazole, copper sulfate and phosphoric acid.

(0015) Dibutylhydroxytoluene, sodium edetate, benzalkonium chloride, citric acid, salicylic acid, isobutyl parahydroxybenzoate, isopropyl parahydroxybenzoate, butyl parahydroxybenzoate, propyl parahydroxybenzoate, methyl parahydroxybenzoate and D-sorbitol are preferable, and dibutylhydroxytoluene, sodium edetate, butyl parahydroxybenzoate, propyl parahydroxybenzoate and methyl parahydroxybenzoate are particularly preferable. The most preferable preservative is dibutylhydroxytoluene.

(0016) The preservative content in the composition is preferably 0.01 to 50 mass percent, more preferably 0.02 to 30 mass percent, and particularly preferably 0.05 to 10 mass percent.

(0017) (D) The aqueous skin external preparation composition of the present invention has an aqueous solvent that contains a monovalent lower alcohol with a carbon number of 1 to 6, and the content of this alcohol is at most 70 mass percent in the composition, preferably 5 to 70 mass percent, more preferably 10 to 60 mass percent, and particularly preferably 20 to 50 mass percent. The solution stability and the suppression of skin irritation are favorable within this range. An aqueous solvent for which the ratio of monovalent lower alcohol with a carbon number of 1 to 6 to water is 0.7 to 1.4 is

preferably used as a solvent. Examples of monovalent lower alcohols include ethanol, isopropanol, n-propanol, butanol and isobutanol. Ethanol, isopropanol and n-propanol are preferable. It is preferable for the lower alcohol to be a mixed alcohol of two or more types, and particularly favorable composition stability can be achieved with a mixed alcohol comprising ethanol and isopropyl alcohol. A mixture with an ethanol/isopropanol ratio (mass ratio) of 0.7 to 10 – particularly a mixture with a ratio of 1 to 8 – yields particularly favorable stability and is thus preferable.

(0018) Various types of denatured alcohols (methanol denatured alcohol, geraniol denatured alcohol, sucrose octaacetate denatured alcohol, denatonium benzoate denatured alcohol, brucine denatured alcohol, etc.) can be used as ethanol.

(0019) In addition to the above constituents, the aqueous skin external preparation composition of the present invention can contain the following constituents within a scope that does not diminish the effect of the present invention.

(0020) (E) Surfactant

A surfactant can be used for the purpose of further improving the liquidity of the aqueous solution of the present invention. Anionic surfactants, cationic surfactants, nonionic surfactants and amphoteric surfactants can be used, but nonionic surfactants and amphoteric surfactants are preferable.

(0021) Examples of nonionic surfactants include ether compounds such as polyoxyethylene alkyl ether and polyoxyethylene polypropylene alkyl ether, ester compounds such as sorbitan fatty acid esters, glycerin fatty acid esters, polyglycerin fatty acid esters, polyoxyethylene glycerin fatty acid esters, polyethylene glycol fatty acid esters and sucrose fatty acid esters, polyoxyethylene castor oil/hardened castor oil, and polyoxyethylene polyoxypropylene polymers.

(0022) Examples of amphoteric surfactants include alkyl betaines such as lauryl dimethyl betaine, alkyl amide betaines such as palm oil fatty acid amidopropyl betaine, alkyl sulfobetaines and imidazolines.

(0023) Examples of anionic surfactants include saturated higher fatty acid salts, alkyl sulfonic acid salts, alkyl ether sulfonic acid salts and alkyl ether sulfonic acid salts [*sic*]. One type or two or more types of these can be used in combination.

(0024) Examples of cationic surfactants include quaternary ammonium salts such as trimethylalkyl ammonium chloride and alkyl amine salts such as dimethylalkyl amine hydrochloride.

(0025) The amount mixed into the composition is preferably in the range of 0.01 to 10 mass percent and more preferably in the range of 0.05 to 5 mass percent.

(0026) (F) Thickener

A thickener can be mixed into the aqueous external preparation composition of the present invention as necessary. A water-soluble polymer or a cross-linking form thereof is preferably used as a thickener. Specific examples include cellulose derivatives such as hydroxypropylcellulose, hydroxypropylmethylcellulose, carmellose, cross carmellose and methylcellulose, processed starches such as partial alpha starch, polyvinyl alcohol, polyvinyl pyrrolidone, cross povidone, polyethylene glycol, carboxyvinyl polymers, acrylic acid/methacrylic acid alkyl copolymers, xanthan gum, carrageenan, sodium alginate, gum arabic, cyamoposis gum, locust bean gum, pullulan, gelatin and sodium polyacrylate. These can be used alone or in combinations of two or more types.

(0027) The amount to be mixed is selected appropriately depending on the preset viscosity of the preparation, but particularly favorable viscosity properties can be obtained when the amount is in the range of 0.01 to 5 mass percent in the composition and preferably in the range of 0.05 to 2 mass percent.

(0028) (G) Drugs

In addition to the anti-inflammatory agent of the present invention, drugs such as antipruritic agents, antihistamines, local anesthetics and blood circulation promoters can be contained.

① Antipruritic agents: Crotamiton, etc.

② Antihistamines: Diphenhydramine and salts thereof, chlorpheniramine and salts thereof, etc.

③ Local anesthetics: Ethyl aminobenzoate, lidocaine and salts thereof, dibucaine and salts thereof

④ Blood circulation promoters: Capsaicin, capsicum, tocopherol acetate, etc.

⑤ Germicides: Acrynol, isopropyl methylphenol, chlorhexidine hydrochloride, chlorhexidine gluconate, phenol, resorcin, sulfur, etc.

⑥ Antibacterial agents: Sulfur agents such as sulfadiazine, sulfisomidine and homosulfamine, etc.

⑦ Antifungal agents: Miconazole nitrate, econazole nitrate, ciclopirox, olamine, clotrimazole, pyrrolnitrin, etc.

⑧ Analgesic agents: Methyl salicylate, aspirin, aminopyrine, acetaminophen, ethenzamide, etc.

⑨ Keratin softeners: Urea, etc.

▲10▼ Vitamins: Ascorbic acid, aqueous vitamins such as pyridoxine hydrochloride, tocopherol, tocopherol acetate, palmitic acid, retinol, oil-soluble vitamins such as vitamin A oil, etc.

▲11▼ Mucopolysaccharides: Heparin analogs or sodium chondroitin sulfate, etc.

▲12▼ Acidic amino acids: Neutral amino acids such as glycin and alanine, aromatic amino acids such as tryptophan and phenylalanine, basic amino acids such as histidine and arginine, aspartic acid, glutamic acid, etc.

The medicinal constituents can be used alone or as a combination of two or more types as necessary. The amounts to be mixed are determined appropriately for each drug.

(0029) (H) Polyvalent alcohol

It is preferable to immix a polyvalent alcohol for the purpose of improving the moisture retention of the skin when applied to the skin. Examples of polyvalent alcohols include ethylene glycol, diethylene glycol, propylene glycol, butylene glycol, dibutylene glycol, glycerin, diglycerin, polyglycerin, sugars such as sucrose, lactose, maltose, mannitol, erythritol and xylitol, sugar alcohols, etc. The polyvalent alcohol content in the composition can preferably be in the range of 0.1 to 30 mass percent and more preferably in the range of 1 to 20 mass percent.

(0030) (I) Oily constituents

The following substances, for example, can be used for oily constituents other than (B). Hydrocarbons such as liquid paraffin, vaseline and microcrystalline wax, silicon oils such as methylpolysiloxane, methylphenylpolysiloxane and dimethylcyclopolysiloxane, waxes such as beeswax, higher alcohols such as cetyl alcohol and stearyl alcohol, sterols such as cholesterol, fatty acid esters such as octyldodecyl oleate, oleyl oleate, cetyl octanoate and isopropyl myristate, and metallic soaps such as aluminum stearate and magnesium stearate, etc. These can be used alone or in combinations of two or more types. The amount to be mixed into the composition can be in the range of 0.05 to 50% and preferably in the range of 0.1 to 30 mass percent.

(0031) (J) Inorganic powder

Stratified silicate minerals such as talc, kaolin, bentonite and aluminum magnesium silicate, titanium oxide, zinc oxide, etc.

(0032) (K) Organic powder

Spherical powders such as nylon, silica and methyl polymethacrylate, polyethylene beads, cellulose powders, starches, etc.

(0033) In addition, "homogeneous" in the present invention indicates that the composition is homogeneously dissolved or soluble rather than emulsified, and a solid organic or inorganic powder such as (J) or (K) may be dispersed into this.

(0034) (L) pH regulator

The aqueous skin external preparation composition of the present invention is preferably regulated to pH 3 to 8 and more preferably to 4 to 7. Examples of pH regulators include hydrochloric acid, lactic acid, sodium hydroxide, potassium hydroxide, triethanolamine, diisopropanolamine and calcium hydrogen phosphate. Diisopropanolamine is preferable because the pH stability is particularly favorable when an acidic drug is used. The quantity of the pH regulator can be selected appropriately based on the preset pH level.

(0035) (M) Chelating agent

Pyrophosphate, hexametaphosphate, gluconate, etc.

[*sic*] (N) Pigments

(N) pigment [*sic*] acidic dyes, basic dyes and oxidation dyes, etc., can be used as desired.

(0036) (O) Fragrance

Examples include plant fragrances such as peppermint oil, spearmint oil, mentha oil, eucalyptus oil, jasmine oil, lavender oil, lemon oil, orange oil, lime oil, mandarin oil, rose oil and rosemary oil and synthetic fragrances such as monoterpenes, diterpenes and sesquiterpenes. Specific examples include menthol, borneol, geraniol, linalool, citronellol, nerol, limonene, pinene, camphene, citral, citronellal, cineol, curcumene, sabinic acid, hinokiol and phytol.

(0037) When the composition of the present invention is a liquid lotion with relatively low viscosity (1 to 1000 cp), it is preferable for the container to have an outflow opening or a discharge opening with a diameter of 0.1 to 5 mm. The opening may be a part of the container or may be a cap or inner plug that can be easily attached and removed. For example, the composition can be stored in a container provided with an inner plug or cap made of resin having at least one hole. It is preferable for the inner plug or cap to have a liquid dripping prevention mechanism such as grooves established on the surface so that the liquid does not run off to the outside wall or a mechanism for preventing the return of liquid to the inside of the container in which the periphery of the hole is given a concave structure toward the top or a backflow prevention valve is installed. Preferable examples include a spray container or squeeze container provided with an application cap or inner plug with a cloth or porous material serving as the application part on the top of the hole is formed, or an inner plug or cap having a discharge mechanism with a discharge hole diameter of 0.1 to 0.5 mm.

(0038) Examples of materials for the inner plug, cap and discharge container nozzle include resins such as PET, polypropylene (PP), polyethylene (high-density polyethylene: HDPE, low-density polyethylene: LDPE) and polystyrene. One type or two or more types of the above materials can be used in combination. When a porous application part is established on the inner plug or cap, it is preferable for the application part to be a cloth or porous natural rubber and a porous material such as urethane foam, a sponge, or a ceramic sintered material.

(0039) Examples of materials for the main body of the container include PET, polypropylene (PP), polyethylene (high-density polyethylene: HDPE, low-density polyethylene: LDPE), glass, polystyrene, and metals such as aluminum. One type or two or more types of these materials can be used in combination.

(0040) When the composition of the present invention has relatively high viscosity (500 to 100,000 cp), it can be preferably stored in a container such as a tube or a bottle. In the case of a bottle, it is preferable for a resin having flexibility to be used. Examples of materials include PET, polypropylene (PP) and polyethylene (high-density

polyethylene: HDPE, low-density polyethylene: LDPE). Examples of tube materials include flexible polyethylene (high-density polyethylene: HDPE, low-density polyethylene: LDPE) and aluminum. A monolayer or multilayer tube of the above materials can be used, or one type or two or more types of the materials described above can be combined to form a laminate tube, etc.

(0041)

(EMBODIMENTS) The aqueous skin external preparation composition of the present invention will be described hereafter through concrete embodiments. The compositions of the embodiments and comparative examples below were prepared and evaluated by performing various tests.

(0042) <Preparation method> Each preparation with a pH level of 4 to 9, which is typical of skin external preparations, was prepared in accordance with a conventional procedure, and each was filled into a polypropylene container with a natural rubber sponge as the application part.

<Sensitivity tests> Tests were performed by applying samples to the forearm in a temperature-controlled room with a room temperature of 20°C and 65% humidity. The samples were evaluated using the following assessment criteria. Evaluations were made using the three levels described below, and ○ or higher was assessed as a satisfactory level.

(◎: no irritation, ○: practically no irritation, × irritation experienced)

<Storage stability> The samples were stored in clear PET containers, and the appearance and odor of the compositions were investigated after one month of storage at 5°C.

(◎: clear, ○: almost completely clear (slightly pale), △: extremely weak turbidity, ×: turbidity)

(◎: odorless, ○: almost completely odorless, △: slightly abnormal odor, ×: abnormal odor)

<Secondary contamination tests> After the samples were applied three times per day for one month, microbial tests were performed on the inner plug of the containers and the contents. The evaluation parameters were the microorganism counts (total number of bacteria and fungi) of the inner plugs and the contents. Evaluations were made using the three levels described below, and ○ or higher was assessed as a satisfactory level.

(◎: microorganism count on the order of 10^1 or lower, ○: microorganism count on the order of 10^2 to 10^3
×: microorganism count on the order of 10^4 or higher)

(0043)

(Table 1)

	1	2	3	4	5	6	7	8
Ketoprofen	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Oleic acid	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Oleyl alcohol	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Menthol	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Dibutylhydroxytoluene	0.05							
Benzalkonium chloride		0.05						
Methylparaben			0.1	0.05				
Propylparaben				0.05				
Sorbitol					1.0			
Sodium edetate						0.2		
Citric acid							1.0	
Salicylic acid								1.0
Diisopropanolamine	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Ethanol	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Isopropanol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Purified water (remaining volume)	52.6	52.6	52.1	52.1	51.2	51.1	51.2	51.2
Skin irritation	◎	◎	◎	◎	◎	◎	◎	◎
Rough skin improvement	◎	◎	◎	◎	◎	◎	◎	◎
Storage stability	◎	◎	◎	◎	◎	◎	◎	◎
Content odor	◎	◎	◎	◎	◎	◎	◎	◎
Secondary contamination tests: Inner plug	◎	◎	○	◎	○	◎	◎	○
: Contents	◎	◎	○	◎	○	◎	◎	○

(0044) (Table 2)

	9	10	11	12	13	14	15	16
Indomethacin	1.0							1.0
Glycyrrhetinic acid		0.2					0.2	
Bufexamac			1.0					
Suprofen				1.0				
Glycol salicylate					2.0			
Heparin analog						0.3	0.3	0.3
Oleic acid	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Oleyl alcohol	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Menthol	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Dibutylhydroxytoluene	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Diisopropanolamine	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Ethanol	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Isopropanol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Purified water (remaining volume)	54.6	55.4	54.6	54.6	53.6	55.3	55.1	54.3
Skin irritation	◎	◎	◎	◎	◎	◎	◎	◎
Rough skin improvement	◎	◎	◎	◎	◎	◎	◎	◎
Storage stability	◎	◎	◎	◎	◎	◎	◎	◎
Content odor	◎	◎	◎	◎	◎	◎	◎	◎
Secondary contamination tests: Inner plug	◎	◎	◎	◎	◎	◎	◎	◎
: Contents	◎	◎	◎	◎	◎	◎	◎	◎

(0045)

(Table 3)

	17	18	19	20	21	22	23	24
Ketoprofen	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Oleic acid	1.0							
Trisorbitan oleate			1.0					
Monosorbitan oleate				1.0				
Glycerin oleate					1.0			
Eicosenic acid								
Myristoleic acid						0.8		0.8
Oleyl alcohol		1.0					1.0	0.2
Myristoleyl alcohol						0.2		
Menthol	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Dibutylhydroxytoluene	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
Diisopropanolamine	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Ethanol	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Isopropanol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0
Purified water (remaining volume)	52.6	52.6	52.6	52.6	52.6	52.6	52.6	52.6
Skin irritation	◎	◎	◎	◎	◎	◎	◎	◎
Rough skin improvement	○	○	○	○	○	◎	○	◎
Storage stability	◎	◎	◎	◎	◎	◎	◎	◎
Content odor	◎	◎	◎	◎	◎	◎	◎	◎
Secondary contamination tests: Inner plug	◎	◎	◎	◎	◎	◎	◎	◎
: Contents	◎	◎	◎	◎	◎	◎	◎	◎

Similarly favorable evaluations were achieved with the other drugs (Table 2).

(0046)

(Table 4)

Composition (g/100 g)	25	26	27	28	29	30	31	32
Ketoprofen	3.0	3.0	3.0	3.0	3.0	3.0	2.0	2.0
Oleic acid	0.8	0.8	0.8	0.8	0.8	0.8	0.5	0.2
Oleyl alcohol	0.2	0.2	0.2	0.2	0.2	0.2	0.5	0.8
Menthol	3.0	3.0	3.0	3.0	3.0	3.0		
Dibutylhydroxytoluene	0.05	0.05	0.05	0.05	0.1	0.1		
Sodium edetate	–	–	–	–			0.2	
Citric acid								1.0
Diisopropanolamine	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Ethanol	20.0	30.0	35.0	35.0	40.0	40.0	35.0	35.0
Isopropanol	20.0	10.0	5.0	10.0	10.0	5.0	10.0	10.0
Purified water (remaining volume)	52.6	52.6	52.6	47.6	42.6	47.6	47.4	46.6
Skin irritation	◎	◎	◎	◎	○	◎	◎	◎
Rough skin improvement	◎	◎	◎	◎	◎	○	◎	○
Storage stability	◎	◎	○	◎	◎	○	◎	◎
Content odor	◎	◎	◎	◎	◎	◎	◎	○
Secondary contamination tests: Inner plug	◎	◎	◎	◎	◎	◎	◎	○
: Contents	◎	◎	◎	◎	◎	◎	◎	◎

(0047)

(Table 5)

Composition (g/100 g)	33	34	35	36	37	38	39	40
Ketoprofen	3.0	3.0	3.0	0.3	3.0	5.0	7.0	5.0
Glycyrrhetinic acid								0.2
Heparin analog								0.3
Oleic acid	3.0	2.0	1.0	0.8	0.8	0.8	0.8	4.9
Oleyl alcohol	1.0	2.0	2.0	0.2	0.2	0.2	0.2	
Menthol	3.0	3.0	3.0	3.0	3.0	3.0	3.0	
Dibutylhydroxytoluene	0.05	0.05	0.05	0.05	0.05	0.1	0.1	
Diisopropanolamine	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Glycerin	5.0	5.0	5.0	5.0				
Propylene glycol					5.0	5.0	5.0	5.0
Ethanol	10.0	10.0	10.0	10.0	40.0	10.0	10.0	10.0
Isopropanol	30.0	30.0	30.0	30.0		30.0	30.0	30.0
Purified water (remaining volume)	44.6	44.6	45.6	50.3	47.6	45.6	43.6	43.6
Skin irritation	◎	◎	◎	◎	◎	◎	○	○
Rough skin improvement	◎	◎	○	◎	◎	◎	◎	○
Storage stability	◎	◎	◎	◎	△	◎	◎	◎
Content odor	◎	◎	◎	◎	◎	◎	◎	◎
Secondary contamination tests: Inner plug	◎	◎	◎	◎	◎	◎	◎	◎
: Contents	◎	◎	◎	◎	◎	◎	◎	◎

The compositions described above were aqueous skin external preparations with extremely favorable moisture retention.

(0048) (Embodiment 41) Anti-inflammatory and analgesic lotion

An anti-inflammatory and analgesic lotion with the following composition (viscosity: 9 cp) was stored in a polypropylene container having a urethane sponge application part (head space: 10%). This was also stored in a similar container with an application part made of foam rubber.

Ketoprofen	3.0
Oleic acid	0.8
Oleyl alcohol	0.2
1-Menthol	3.0
Glycerin	5.0
Sucrose octaacetate denatured alcohol	40.0
Isopropyl alcohol	10.0
Hydroxypropylcellulose	0.5
Dibutylhydroxytoluene	0.05
Diisopropanolamine	0.5
Eucalyptus oil	0.1
Purified water	Remaining volume

(0049) (Embodiment 42) Anti-inflammatory and analgesic lotion

An anti-inflammatory and analgesic lotion with the following composition (viscosity: 8 cp) was stored in a polypropylene container provided with a polypropylene inner plug having a hole with a diameter of 1 mm in the bottle (head space: 10%).

Ketoprofen	3.0
Oleic acid	0.8
Oleyl alcohol	0.2
1-Menthol	3.0
1-3-Butylene glycol	5.0
Sucrose octaacetate denatured alcohol	37.0
Isopropyl alcohol	10.0
Hydroxypropylcellulose	0.5
Dibutylhydroxytoluene	0.05
Diisopropanolamine	0.5
Purified water	Remaining volume

(0050) (Embodiment 43) Anti-inflammatory and analgesic spray

An anti-inflammatory and analgesic solution with the following composition (viscosity: 10 cp) was stored in a manual spray container having a discharge opening with a diameter of 0.45 mm

(head space: 10%).

Ketoprofen	3.0
Camphor	1.0
Oleic acid	0.8
Oleyl alcohol	0.2
1-Menthol	3.0
1-3-Butylene glycol	5.0
Orange denatured alcohol	35.0
Isopropyl alcohol	10.0
Hydroxypropylcellulose	0.5
Dibutylhydroxytoluene	0.05
Diisopropanolamine	0.5
Lemon oil	0.1
Rosemary oil	0.1
Purified water	Remaining volume

(0051) (Embodiment 44) Anti-inflammatory and analgesic aerosol

The following anti-inflammatory and analgesic solution (viscosity: 7 cp) was stored in an aluminum aerosol can with a polystyrene nozzle to form an aerosol.

(Units: g/100 g)

(Undiluted solution) 80 parts

Indomethacin	0.75
1-Menthol	1.0
Oleic acid	0.5
Oleyl alcohol	0.5
Hydroxypropylcellulose	0.4
Ethanol	48.0
Propylene glycol	5.0
Triethanolamine	0.8
Dibutylhydroxytoluene	0.05
1-3-Butylene glycol	5.0
Polyoxyethylene hardened castor oil	0.5
Isopropyl myristate	0.5
Mint oil	0.1
Purified water	39.0

(Spray agent) 20 parts

Dimethyl ether	100

(0052) (Embodiment 45) Insect bite gel

An insect bite gel with the following composition (viscosity: 10,000 cp) was stored in a polyethylene tube.

Diphenhydramine	2.0
Methyl salicylate	2.0
Monoglycerin oleate	1.0
Brucine denatured ethanol	25.0
Isopropanol	10.0
Sodium edetate	0.1
Citric acid	0.3
Hydroxyethylcellulose	1.5
Propylene glycol	10.0
Diisopropanolamine	0.2
Rose oil	0.1
Purified water	Remaining volume

(0053) (Embodiment 46) Antipruritic lotion (viscosity: 5 cp)

(Container: Polyethylene container with a natural rubber sponge inner plug)

Urea	10.0
Crotamiton	5.0
Diphenhydramine	1.0
Glycyrrhetinic acid	0.5
Lactic acid	2.0
Oleic acid	0.1
Denatonium benzoate denatured alcohol	20.0
Isopropyl alcohol	12.0
Sodium edetate	0.1
Potassium hydroxide	2.3
Triethanolamine	0.8
Eucalyptus oil	0.2
Mentha oil	0.3
Purified water	Remaining volume

(0054) (Embodiment 47) Muscular pain gel (viscosity: 18,000 cp)

(Container: Polypropylene container with a PET inner plug, opening diameter: 3 mm)

Ketoprofen	3.0
1-Menthol	3.0
Oleic acid	0.5
Oleyl alcohol	0.1
Acrylic acid/methacrylic acid alkyl copolymer (BF Goodrich Carbopol 1382)	2.0
Ethanol	25.0
Isopropyl alcohol	15.0
1,3-Butylene glycol	5.0
Triethanolamine	0.5
Rosemary oil	0.2
Purified water	Remaining volume

(0055) (Embodiment 48) Back pain gel (viscosity: 14,000 cp)

(Container: Polypropylene container with a polystyrene inner plug, opening diameter: 5 mm)

Indomethacin	0.75
1-Menthol	3.0
Oleic acid	0.5
Carboxyvinyl polymer (BF Goodrich Carbopol 1981)	2.0
Ethanol	40.0
Isopropyl alcohol	5.0
Diisopropanolamine	0.5
Purified water	Remaining volume

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